Bioorganic & Medicinal Chemistry 21 (2013) 6893–6909

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of novel 3,5-bis-*N*-(aryl/heteroaryl) carbamoyl-4-aryl-1,4-dihydropyridines as small molecule BACE-1 inhibitors

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ARTICLE INFO

Article history:
Received 8 July 2013
Revised 4 September 2013
Accepted 12 September 2013
Available online 20 September 2013

Keywords:
Alzheimer
BACE-1
Dihydropyridine
Virtual screening

ABSTRACT

Alzheimer disease (AD) is a neuronal dementia for which no treatment has been consolidated yet. Major pathologic hallmark of AD is the aggregated extracellular amyloid-β plaques in the brains of disease sufferers. Aβ-peptide is a major component of amyloid plaques and is produced from amyloid precursor protein (APP) via the proteolysis action. An aspartyl protease known as β-site amyloid precursor protein cleaving enzyme (BACE-1) is responsible for this proteolytic action. Distinctive role of BACE-1 in AD pathogenesis has made it a validated target to develop anti-Alzheimer agents. Our structure-based virtual screening method led to the synthesis of novel 3,5-bis-*N*-(aryl/heteroaryl) carbamoyl-4-aryl-1,4-dihydropyridine BACE-1 inhibitors (**6a**–**6p**; in vitro hits). Molecular docking and DFT-based ab initio studies using B3LYP functional in association with triple-ζ basis set (TZV) proposed binding mode and binding energies of ligands in the active site of the receptor. In vitro BACE-1 inhibitory activities were determined by enzymatic fluorescence resonance energy transfer (FRET) assay. Most of the synthesized dihydropyridine scaffolds were active against BACE-1 while **6d**, **6k**, **6n** and **6a** were found to be the most potent molecules with IC_{50} values of 4.21, 4.27, 4.66 and 6.78 μM, respectively. Superior BACE-1 inhibitory activities were observed for dihydropyridine derivatives containing fused/nonfused thiazole containing groups, possibly attributing to the additional interactions with S2–S3 subpocket residues. Relatively reliable correlation between calculated binding energies and experimental BACE-1 inhibitory activities was achieved (R^2 = 0.51). Moreover, compounds **6d**, **6k**, **6n** and **6a** exhibited relatively no calcium channel blocking activity with regard to nifedipine suggesting them as appropriate candidates for further modification(s) to BACE-1 inhibitory scaffolds.

1. Introduction

Alzheimer disease (AD) is a neurodegenerative disorder clinically recognized by progressive decline in memory and cognition.[1] AD accounts for most cases of dementia in the elderly population.[2,3] Histological examination of the brains of affected individuals has revealed the existence of significant synaptic loss.[4] The main neuropathological characteristics of AD are the presence of extracellular amyloid plaques and intracellular Neurofibrillary tangles (NFT) in the brain. The amyloid plaques result from the deposition of aggregated amyloid beta (Aβ) peptides. Aβ peptides (mainly as $Aβ_{40}$ and $Aβ_{42}$) are the product of two consecutive proteolytic cleavages on a large trans-membrane protein; amyloid precursor protein (APP).

By 1999, various independent researchers discovered BACE-1 as the aspartyl protease β-site APP-cleaving enzyme. BACE-1 initiates the amyloid cascade by cleavage of APP.[5,6] Subsequent cleavage of the C-terminus of APP by γ-secretase results in the formation of $Aβ_{40}$ and $Aβ_{42}$. In the nonamyloidogenic pathway, α-secretase cleaves APP leading to the generation of neuroprotective peptide sAPPα.[7]

Inhibition of β and γ-secretase enzymes by small molecule blockers is a promising approach to find therapeutic agents for AD. In this regard, inhibition of β-secretase is very importance since several studies have shown that inhibition of γ-secretase may have some mechanism-based adverse effects.[8,9] The strategy of BACE-1 blockade for AD-therapy has been further supported by the observation of normal phenotype in BACE-1 knockout mice.[10]

Many research groups have focused on the development of BACE-1 inhibitors.[11,12] BACE-1 inhibitors were primarily designed

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0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.09.033